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13. ABSTRACT (Maximum 200 Words)

The objective of this Career Development Award (CDA) is to evaluate the gene-gene and gene-environment interactions in the etiology of breast cancer in two ongoing case-control studies, the Shanghai Breast Cancer Study (SBCS) and the Nashville Breast Health Study (NBHS), and in one newly proposed case-control study, the Breast Cancer in West Africa Study (BCWAS). The work in the first year of this CDA has resulted in a study from the SBHS titled: "Genetic polymorphisms in uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) and risk of breast cancer", presented at the American Association for Cancer Research (AACR) molecular epidemiology of cancers meeting in Waikoloa, HI in January 2003 and a draft manuscript to be submitted for publication in the early part of the second year of the award. The awardee participated in the conduct of the NBHS and in the development of its full-study funding proposal re-submitted to the National Cancer Institute in March 2003. Funding was obtained from the institutional cancer alliance between Meharry Medical College and Vanderbilt-Ingram Cancer Center to conduct the pilot project of the BCWAS for two years starting in May 2003.

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Gene-gene and gene-environment interactions in the etiology of breast cancer (DAMD17-02-1-0482)

First Year Report, June 2003

Introduction

Breast cancer is the most common form of cancer (other than skin) and a leading cause of cancer mortality among women in the United States (1). The two known major susceptibility genes, *BRCA1* and *BRCA2*, do not explain a significant proportion of familial breast cancer (2). Most breast cancer has a complex, multifactorial etiology (3). It is still unclear the number and nature of genetic variants that predispose women to breast cancer, and the interplay between these variants and environmental factors (4). Recent studies have not shown any consistency in the association of known genetic polymorphisms and breast cancer risk (5). Most of these studies have had small sample sizes and subjects have been predominantly Caucasians (5-7). Studies to detect interactions typically require large sample sizes (7). Differences in behavioral and cultural attitudes, ethnicity, economic status, and lifestyle influences among different groups of women require further study to determine how these factors contribute to enhancing or reducing breast carcinoma risk (8). The main objective of this Career Development Award (CDA) is to evaluate the contributions of gene-gene and gene-environment interactions in the etiology of breast cancer in three population-based case-control studies of breast cancer risk by: 1) evaluating the gene-gene and gene-environment interactions in the study cohort of the ongoing Shanghai Breast Cancer Study (SBHS), 2) evaluating the role of genetic factors, gene-gene interaction, and gene-environment interaction in the study cohort of the ongoing Nashville Breast Health Study (NBHS), and 3) investigating the association of breast cancer with lifestyle factors and environmental exposures and evaluate the role of genetic factors, gene-gene interaction, and gene-environment interaction in the proposed Breast Cancer in West Africa study (BCWAS). The results of these large studies we hope will contribute to understanding the association between lifestyle, environmental, and genetic factors with breast cancer. By understanding the complex interplay and effects of genes with one another and with environmental factors, it may be possible to improve risk assessment and the potential for targeted cancer prevention strategies.

Body

In collaboration with many other investigators, the work that I have accomplished during the first year of this CDA are described below the specific tasks that had been outlined in the approved Statement of Work as shown below:

Task 1. **To collate phenotype and genotype information on the on-going Shanghai Breast Cancer Study (SBCS) participants and conduct analyses of the Shanghai Breast Cancer Study for two-level gene-gene and gene-environment interactions, (Months 1-24):**

The SBHS conducted its first round of recruitment of 1,459 breast cancer cases and 1,560 age-frequency matched controls in Shanghai from August 1996 to March 1998. The SBHS is presently conducting a second phase of recruitment of participants to increase its study sample size to 3,000 breast cancer cases and 3, 000 controls.

a. Collation and editing of phenotype information of all SBCS participants from already completed in-person interviews into a database (Months 1-3).

We completed the collation into a database and edit of the available phenotype information of 1,459 cases and 1,556 controls in preparation for data analyses as proposed within the first three months of the first year.

b. Collation of genotype information of all the SBCS participants for all the genes that genotyping assays have been completed (Months 4-6).

The genotyping work has been ongoing and has been completed for 5 functional polymorphisms. The first polymorphism specifically we selected for study in this CDA was the *UGT1A1*28* polymorphism. Uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) is involved in catalyzing estrogen, the hormone that plays a central role in the etiology of breast cancer. A common polymorphism [$A(TA)_6TAA$ (allele *1) to $A(TA)_7TAA$ change (allele*28)] in the TATA-box of the promoter region of the *UGT1A1* gene has been reported to have possible influences on the transcription of this gene. The UGT1A1 genotyping was completed in Dr. Zheng's laboratory at Vanderbilt University Medical Center, Nashville, TN (VUMC). Genotyping data were obtained from 1,047 (87.8%) cases and 1,082 (82.6%) controls that had blood samples. The major reasons for incomplete genotyping were insufficient DNA and unsuccessful polymerase chain reaction (PCR).

c. In collaboration with Dr. Wei Zheng, conduct analyses and prepare manuscripts of the association of estrogen metabolic genes with breast cancer in the Shanghai Breast Cancer Study (Months 7-18).

The PI of this CDA (Dr. Adegoke) completed the analyses for investigating the association of *UGT1A1*28* polymorphism with the risk of breast cancer among 1,047 breast cancer cases and 1,082 community controls in the SBCS and the evaluation of the relationship of UGT1A1 genotypes with plasma levels of estrone, estrone sulfate, estradiol, testosterone, and sex hormone binding globulins (SHBG) among 375 postmenopausal controls that were measured for these molecules. The results of these analyses were presented at the American Association for Cancer Research (AACR) "Molecular and Genetic Epidemiology of Cancer" (AACR Special Conferences in Cancer Research) Meeting, held from January 18-23, 2003, in Waikoloa, HI. In addition, we have prepared a manuscript draft of the results titled "**Genetic polymorphisms in uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) and risk of breast cancer**". This manuscript draft is presently undergoing review by the co-authors for final submission to the *Cancer Epidemiology, Biomarkers & Prevention* (CEBP) journal for publication consideration. The abstract for this work is attached in the appendix to this report. A second set of data analyses that will result in a manuscript is to be completed in the second year of this CDA.

Task 2. **To actively participate in the fieldwork and conduct of the Nashville Breast Health Study and conduct analyses of the NBHS, (Months 1-48):**

The pilot phase of the NBHS is ongoing. We submitted a funding proposal to the National Cancer Institute for the full study phase in March 2003. Due to the recruitment successes recorded so far in the pilot phase, the target enrollment for the NBHS has been increased from 1,000 incident breast cancer cases to 1,500 incident breast cancer cases.

The aims of the NBHS are:
1) To recruit 1500 incident breast cancer cases and 1500 frequency-matched controls in Nashville;
2) To conduct a phone interview to obtain information on NSAID use, well-done meat intake, and other lifestyle factors;
3) To collect exfoliated buccal cell samples through mouth rinsing and extract DNA from these samples;
4) To perform genotyping assays for the polymorphisms of the following genes: *CYP2C9 UGT1A6, UGT1A1, CYP1A1, CYP1B1, NAT1, NAT2, SULT1A1, UGT1A1, GSTA1, GSTM1, GSTP1, GSTT1,* and *COMT*. The polymorphisms of these genes are summarized in Table B1 and discussed in Sections B1 to B7.
5) To perform statistical analysis to evaluate the hypotheses described above;
6) To store DNA samples for future study of other genetic factors.

a. Actively participate in the fieldwork and conduct of the Nashville Breast Cancer Study (NBHS) (Months 1-48).

As of March 1, 2003 we had identified 465 cases from five hospitals in metropolitan Nashville for the NBHS. Of these identified cases, 421 cases have been determined as eligible for participation in the study and 254 of them have been recruited. One of the participating hospitals is the Meharry Medical College (MMC) where the PI of this CDA award is the PI of the NBHS. Dr. Adegoke leads the conduct of this study at MMC as approved by the institution's IRB but has no direct contact with identified potential participants. It is anticipated that we will meet our recruitment objectives as proposed.

b. In collaboration with Dr. Wei Zheng, conduct analyses and prepare manuscripts of the Nashville Breast Health Study (Months 36-48).

There is nothing to report on this task presently, as we are not yet at this stage of the study.

Task 3. **To undergo intensive training in cancer biology, advanced genetic and molecular epidemiology, and statistical genetics, (Months 6-15):**

a. Audit course in Advanced Genetics: Biochemistry and Cell Biology taught by Drs. Scott Hiebert, Wayne Wahls, and Graham Carpenter at Vanderbilt University Medical Center (VUMC) (Months 6-10).
b. Audit course in Cancer Biology taught by Drs. Graham Carpenter, Roy Jensen, and Earl Ruley at VUMC (Months 11-15).
c. Audit course in Cellular and Molecular Basis of Pathology taught by Dr. Gregory Sephel at VUMC (Months 11-15).
d. Audit course in Human Genetics taught by Drs. Jonathan Haines and James Sutcliffe at VUMC (Months 11-15).

e. Audit course in Molecular Aspects of Cancer Research taught by Dr. Graham Carpenter at VUMC (Months 11-15).

On review of this training task by Drs. Adegoke and Zheng, it was determined that Dr. Adegoke had had formal training that involved many of the subject matter covered in the courses that he had proposed to audit under this task. His training as a physician, and a doctoral epidemiologist with focus in cancer epidemiology has provided him with some of the required background for this CDA. In addition, has attended many relevant courses, workshops, and conferences in the past three years that have further served as training for him for this CDA. However, he will be auditing the Cancer Biology course taught by Drs. Graham Carpenter, Roy Jensen, and Earl Ruley at VUMC in the second year of this award and, the Molecular Aspects of Cancer Research taught by Dr. Graham Carpenter in the third year of this award. It has been deemed necessary that he takes both courses at different times to allow him enough time to participate on his other tasks on this award.

Task 4. **To conduct a case-control study of breast cancer risk factors in West Africa, the Breast Cancer in West Africa Study (BCWAS) (Months 24-48):**

Though this task was proposed for the third and fourth year of this award, it was commenced in the first year. Drs. Adegoke and Zheng made two preliminary visits to West Africa in March 2002 (Dr. Adegoke) and June 2002 (Drs. Adegoke and Zheng) to finalize collaboration plans, discuss study protocol development, and start off plans for this study. Dr. Zheng's trip to West Africa with Dr. Adegoke underscore his strong commitment, not only to the success of this proposed study, but also to Dr. Adegoke's development into an independent investigator.

a. Develop and submit a grant proposal for institutional funding or Cancer Center funding of pilot study of breast cancer risk in West Africa (Months 24-28).

A pilot project proposal for the BCWAS was developed and submitted for competitive funding on the Comprehensive Meharry Medical College/Vanderbilt-Ingram Cancer Center Cancer Research Partnership (1 U54-CA9140801) funded by the National Cancer Institute (NCI). Our pilot proposal was awarded a two-year funding starting from May 2003 with the following objectives: a) to develop the protocol for the recruitment of participants and selection of appropriate controls; b) to develop and validate culturally appropriate questionnaires for the collection of demographic, lifestyle history, medical history, reproductive history, family history, and anthropometrics measurements data; c) to develop protocols for the collection, shipment to the United States, and storage of blood samples, cheek cells, and urine samples at Meharry Medical College; d) to determine the response rates for cases and controls by study site and identify strategies to increase participation as required in the larger study; and e) to analyze the preliminary data collected.

b. Develop recruitment strategy, develop manual of procedure for the sites, visit West Africa to meet with collaborators, and ship supplies to commence pilot study of BCWAS (Months 28-32).

We have started working on this task and are in the process of developing recruitment strategies and protocols for the conduct of the pilot study at the two West African study sites.

c. Begin the pilot study of BCWAS with total of 100 cases and 100 controls from 5 study sites at 20 cases and 20 controls from each site (2 sites in Ghana and 3 sites in Nigeria) (Months 33-36).

To be completed in Years 2 and 3 of this award. From our preliminary feasibility visits to the earlier proposed sites we have identified several logistical problems and funding limitations that will constrain us to limit this study to two sites, one in Ghana, and one in Nigeria.

d. In collaboration with senior colleagues, submit a grant to conduct the full phase study of the BCWAS with a total recruitment of 1,500 cases and 1,500 controls (Months 37-40).

To be completed in Year 4 of this CDA.

e. In collaboration with Dr. Wei Zheng and West African collaborators, start the full phase of BCWAS after necessary amendments have been made to study protocol as suggested by the results of the pilot study and ship supplies to study sites (Months 41-48).

The full study of this proposed BCWAS is expected will start before the completion of the fourth year of this CDA.

Task 5. **To conduct a cohort study, The West African Women's Health Study (WAWHS), (Months 36-48):**

a. Identify potential West African collaborators, develop recruitment strategy, draft manual of procedure, and determine logistic requirements (Months 36-42).

b. In collaboration with senior colleagues and West African collaborators, submit a grant to conduct a cohort study of 30,000 women in West Africa, the West African Women Health Study (WAWHS) (Months 43-48).

To be completed in Year 4 of this award.

Key Research Accomplishments

- Participation in the analyses of the SBHS data.
- Participation in the conduct of the pilot phase of the NBHS.
- Participation in the development and submission of the full-study proposal for the NBHS.

Reportable Outcomes

1. Recipient of AACR-HBCU Faculty Scholar Award for Cancer Research to attend the "Frontiers in Cancer Prevention Research", AACR Special Conferences in Cancer Research. Boston, MA. October 14-18, 2002.

2. Recipient of AACR-HBCU Faculty Scholar Award for Cancer Research to attend the "Molecular and Genetic Epidemiology of Cancer", AACR Special Conferences in Cancer Research. Waikoloa, HI. January 18-23, 2003.

3. Recipient of AACR-HBCU Faculty Scholar Award for Cancer Research to attend the 94th Annual Meeting of the American Association for Cancer Research. (AACR), Washington, DC. July 11-14, 2003.

4. **Adegoke OJ**, BeLue R, Gebretsadik T, Ahmed NU. Breast self examination and clinical breast examination in Metropolitan Nashville Health District. "Frontiers in Cancer Prevention Research", AACR Special Conferences in Cancer Research, Boston, MA. (Abstract #B122, October 16, 2002).

5. **Adegoke OJ**, Shu XO, Smith J, Yu H, Jin F, Cai Q, Gao YT, Zheng W. Genetic polymorphisms in uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) and risk of breast cancer. "Molecular and Genetic Epidemiology of Cancer", AACR Special Conferences in Cancer Research, Waikoloa, HI. (Abstract #A11, January 20, 2003).

6. Proposal for pilot project of the Breast Cancer in West Africa Study submitted to the MMC/VICC Comprehensive Cancer Center Research Alliance (1 U54-CA9140801) in February 2003. Funded in May 2003.

7. Proposal for Molecular and Genetic Epidemiology of Breast Cancer Training Program at Meharry Medical College (BC022334) submitted to Department of Defense (U.S. Army) in August 2002. (Investigators: Olufemi Adegoke (PI), Wei Zheng, Ana Grau, Carlos Arteaga, Qiuyin Cai). Not funded.

8. Proposal for full-phase of The Nashville Breast Health Study (RO1 CA100374) re-submitted to NIH in March 2003. (PI: Wei Zheng).

Conclusions

My understanding of the molecular epidemiology of breast cancer has been greatly enhanced by my attendance and poster presentations at many Cancer research meetings in the first year of this CDA. This in turn is quickly enabling me to acquire several experiences that I need to develop into an independent investigator. Results from the investigation of the association of *UGT1A1*28* polymorphism with the risk of breast cancer in Chinese women participating in the SBHS did not indicate a significant role for this polymorphism in the risk of breast cancer. However, in the analysis of hormone levels and UGT1A1 genotype among postmenopausal controls, we observed progressively lower blood levels of estrone (E1) and estrone sulfate (E1-S), and higher levels of testosterone and sex-hormone binding globulins (SHBG) with increasing presence of *28 allele compared to the wild *1/*1 genotype. Our observations suggest that genetic polymorphism in the *UGT1A1* gene is related to the blood levels of SHBG and estrogens and may thus be related to the risk of postmenopausal breast cancer in Chinese women. Efforts are underway to conduct similar analyses for the Caucasian and African-American populations in the NBHS and to the African population in the BCWAS when these studies have recruited large enough participants.

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Appendices

1. **Adegoke OJ**, Shu XO, Smith J, Yu H, Jin F, Cai Q, Gao YT, Zheng W. Genetic polymorphisms in uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) and risk of breast cancer. "Molecular and Genetic Epidemiology of Cancer", AACR Special Conferences in Cancer Research, Waikoloa, HI. (Abstract #A11, January 20, 2003).

2. Abstract of the pilot study of the Breast Cancer in West Africa Study (BCWAS) funded by the Comprehensive Meharry Medical College/Vanderbilt-Ingram Cancer Center Cancer Research Partnership (1 U54-CA9140801) pilot project funds for two years from 05/01/03-04/30/05.

Genetic polymorphisms in uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) and risk of breast cancer

Olufemi J. Adegoke, Xiao-Ou Shu, Jeffrey Smith, Herbert Yu, Fan Jin, Qiuyin Cai, Yu-Tang Gao, Wei Zheng

Meharry Medical College, Nashville, TN[1]; Vanderbilt University Medical Center, Nashville, TN[2]; Yale University School of Medicine, New Haven, CT[3]; Shanghai Cancer Institute, Shanghai[4].

Uridine diphospho-glucuronosyltransferase 1A1 (UGT1A1) is involved in catalyzing estrogen, the hormone that plays a central role in the etiology of breast cancer. A common polymorphism [$A(TA)_6TAA$ (allele *1) to $A(TA)_7TAA$ change (allele*28)] in the TATA-box of the promoter region of the *UGT1A1* gene has been reported to have possible influences on the transcription of this gene. We investigated the association of this *UGT1A1* polymorphism with the risk of breast cancer among 1047 breast cancer cases and 1082 community controls in the Shanghai Breast Cancer Study, a population-based case-control study. Approximately 12.5% of cases and 13.0% of controls carried the variant allele *28. Overall, no difference was observed between cases and controls in the distribution of UGT1A1 genotypes. Among postmenopausal women, a nonsignificant reduced risk for breast cancer was observed for women who carry one *28 allele (odds ratio [OR] = 0.7, 95% confidence interval [CI] = 0.5-1.1). The risk, however, was slightly elevated among subjects who carry two copies of this allele (OR = 1.5, 95%CI = 0.5-4.3); but the sample size was small in this group. No appreciable modifying effect of lifestyle factors was noted on the association between UGT1A1 polymorphism and breast cancer risk. We also evaluated the relationship of *UGT1A1* genotypes with plasma levels of estrone, estrone sulfate, estradiol, testosterone, and sex hormone binding globulins (SHBG) among 375 postmenopausal controls that were measured for these molecules. The geometric means of estrone sulfate (p-trend = 0.02) and estradiol (p-trend = 0.02) were significantly lower in those heterozygous for *28 allele and homozygous for *28 allele than those homozygous for the *1 allele. On the other hand, the mean for SHBG was significantly higher among women who carried one or two copies of the *28 allele than those homozygous for the *1 allele (p-trend <0.01). The results from this study suggest that genetic polymorphism in the *UGT1A1* gene is related to the blood levels of SHBG and estrogens and may thus be related to the risk of postmenopausal breast cancer in Chinese women.

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

In West Africa, the ancestral population of a large proportion of African Americans, the incidence rates of breast cancer have more than doubled over the past two decades. This increase has not been explained by improved diagnostic methods. Most breast cancer has a complex, multi-factorial etiology. The two known major susceptibility genes, BRCA1 and BRCA2, do not explain a significant proportion of familial breast cancer. Cumulative evidence suggests genetic factors and their interaction with lifestyle factors may play an important role in breast cancer etiology. In addition to the well-defined high penetrance genes, over two-dozen genes have been hypothesized to increase the susceptibility to breast cancer. Of note are polymorphic low-penetrance genes that are involved in: a) DNA repair, b) carcinogen metabolism, c) estrogen metabolism (or sex hormone biosynthesis), d) regulation of cell proliferation and apoptosis, e) immuno pathway, and f) iron metabolism pathway. This study may provide insight into the underlying causes for the increasing risk for this malignancy among African American women, other ethnic minorities and underserved populations in the U.S. and other parts of the world.

Our long-term goal is to conduct a large molecular epidemiologic study of lifestyle risk factors, association of low-penetrance genes, and investigation of gene-gene and gene-environment interactions in the risk of breast cancer in women from two West African countries, Ghana and Nigeria. In this pilot, we propose to conduct a two-year case-control study of 200 cases of breast cancer and 200 controls aged 25 to 64 years to evaluate the feasibility of conducting the larger study. From each study site, one site in Ghana, University of Ghana Medical School (UGMS), in Accra, and one site in Nigeria, Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile Ife, we hope to recruit 100 breast cancer cases and 100 age frequency-matched population-based controls.

In the pilot study we propose to: 1) develop the protocol for the recruitment of participants and selection of appropriate controls, 2) develop and validate culturally appropriate questionnaires for the collection of demographic, lifestyle history, medical history, reproductive history, family history, and anthropometrics measurements data, 3) develop protocols for the collection, shipment to the United States and storage of blood samples, cheek cells, and urine samples at Meharry Medical College, TN, 4) determine response rates for cases and controls by study site and identify strategies to increase participation as required in the larger study, and, 5) analyze preliminary data collected. The results from this pilot project will provide clues to refine future hypotheses for our larger study.

PERFORMANCE SITE(S) *(organization, city, state)*

Meharry Medical College, Nashville, TN
Vanderbilt University Medical Center, Nashville, TN
University of Ghana Medical School, Accra, Ghana
Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Nigeria

KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	Organization	Role on Project
Olufemi J. Adegoke	Meharry Medical College	Principal Investigator
Wei Zheng	Vanderbilt University Medical Center	Co-investigator
Gilbert A. B. Amoah	University of Ghana Medical School	Co-investigator/Ghana site PI
Muheez Durosinmi	Obafemi Awolowo University	Co-investigator/Nigeria site PI
Marian O. Ladipo	Meharry Medical College	Study coordinator/Research associate

Disclosure Permission Statement. Applicable to SBIR/STTR Only. See instructions. ☐ **Yes** ☐ **No**